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As part of a multifactorial computer-assisted study of patients with asthma, the relationship between air pollution, animal dander and asthma symptoms was evaluated. No association was found between four major air pollutants (carbon monoxide, ozone, nitrogen oxides and sulfur dioxide) and asthma symptoms. Patients who owned cats and dogs reported more severe asthma symptoms ($p<.01$) than patients who did not own cats and dogs. The evaluations completed to date indicate that daily exposure to cats and dogs accounts for more of the asthma symptoms differences between patients than daily exposure to air pollutants.

A MULTIFACTORIAL STUDY OF PATIENTS WITH ASTHMA. PART 2: AIR POLLUTION, ANIMAL DANDER AND ASTHMA SYMPTOMS

JOHN H. KURATA, Ph.D., M. MICHAEL GLOVSKY, M.D., ROBERT L. NEWCOMB, Ph.D., and JAMES G. EASTON, M.D.

DURING THE LAST two decades interest in air pollution and its effects on diseases has been increasing. It is the belief of many that air pollution aggravates diseases of the upper and lower respiratory tracts, although this has not been established as fact. Specifically, in regards to patients with asthma, conclusions of previous studies indicate that air pollution may affect the severity of this condition. Zweiman et al,[1] in a review of studies on air pollution and asthma, concluded: " . . . it seems reasonable for physicians caring for asthmatic patients to be continually aware of the possibility that air pollution may be an aggravating factor . . . "

The major reasons that more definitive statements about the relevance of air pollution in asthma have not been made are as follows: (1) Most studies which have reported significant results did not classify patients with asthma separately from those with other obstructive bronchopulmonary diseases. Studies which specifically evaluated patients with asthma reported conflicting findings. (2) Most studies were epidemiologic and thus were confounded by the effects of meteorologic components, synergistic effects of other pollutants, pollens, etc.

In this study we are concerned with relationships between asthma and the four measurable air pollutants responsible for pulmonary irritations:[1,2,3,4] sulfur dioxide, oxidants (ozone), nitrogen oxides and carbon monoxide. We have included only patients who have been diagnosed as

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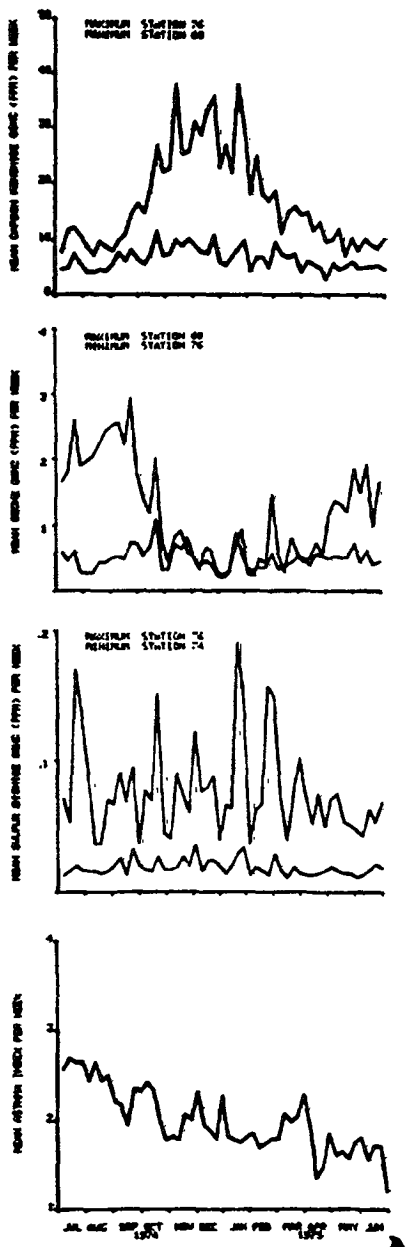
"asthmatic" by the standards described in Part I of this project[5] and thus have avoided the first problem listed above. We have avoided the second problem of failing to consider synergistic pollutant effects by collecting and analyzing data on several types of pollutants concurrently. Finally, in addition to the exposure to air pollutants, we present a preliminary multivariate analysis of concurrent exposure to animals. We will analyze other important factors such as concurrent exposure to pollens and psychological factors at a later date.

Materials and Methods

This section includes only a brief description of the materials and methods relevant to this study, since a more complete description can be found in Part 1.[5] All patients were diagnosed as having asthma on the basis of physical examinations, medical histories and response to bronchodilator medication. Most patients were on regular hyposensitization schedules based on histories and skin test reactivity. There were 20 males and 25 females, ranging from 7 to 72 years of age.

Patients recorded wheezing symptoms, medication for wheezing and other allergy related items daily on punch-card diaries for a period of one year. They mailed the diary cards back weekly and came to the allergy clinic for monthly interviews. Air pollution data from 13 air monitoring stations in the Los Angeles area were supplied by the Los Angeles Air Pollution Control District. The PDP-10 and Sigma-7



Figures 1–4. All graphs display weekly averages for the indicated variables for the common period from July, 1974, through June, 1975. The first three graphs contrast the stations reporting the maximum and minimum year-long concentrations. The last graph reports the average Asthma Index for all patients in the study.

computers at the University of California, Irvine, were used to analyze the data.

*Asthma Index = (Day wheeze + Night wheeze + Medication for wheezing) The Formula for this index has been shortened to only three symptom variables. The range of values for this index is 0-9.

**The average concentration is based upon the mean of the daily instantaneous maxima for each station from July, 1974, to June, 1975.

Results

The weekly average of pollutants for all 13 stations and the weekly average of the Asthma Index* were plotted for July, 1974, through June, 1975. For the sake of brevity data from only the stations with the highest average concentrations and the stations with the lowest average concentrations** for each pollutant are pre-

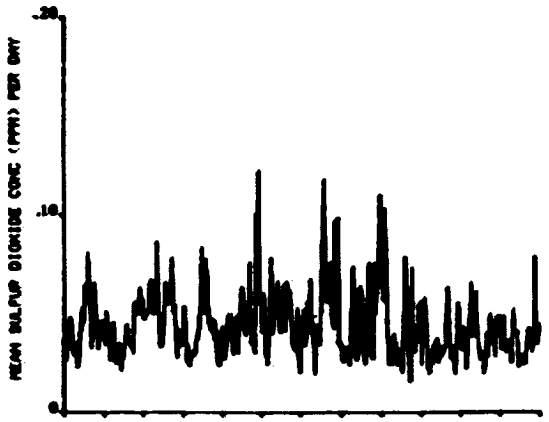


Figure 5. Mean sulfur dioxide concentrations in parts per million (PPM) per day for July, 1974, through June, 1975.

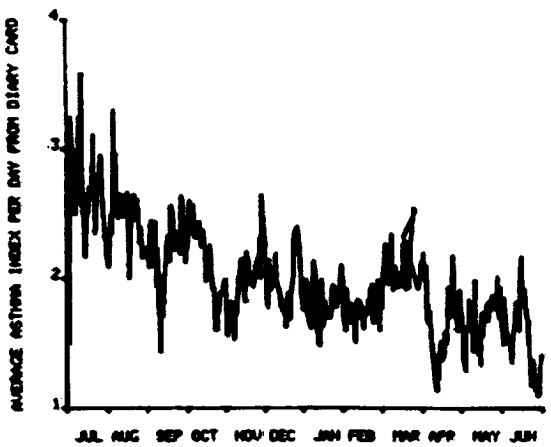


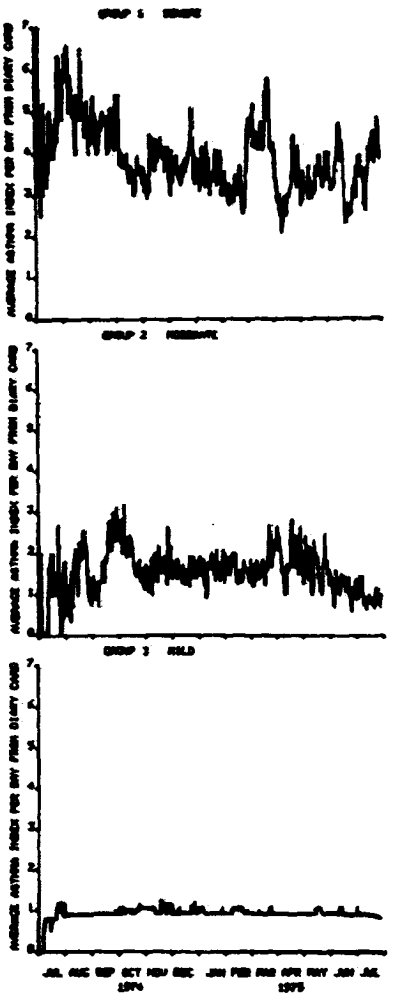
Figure 6. Mean Asthma Index per day for July, 1974, through June, 1975.

sented in Figures 1 through 3. A plot of the weekly average Asthma Index for all patients combined is presented in Figure 4. Visual examination of these figures does not reveal any marked or consistent relationships between pollutants and symptoms.

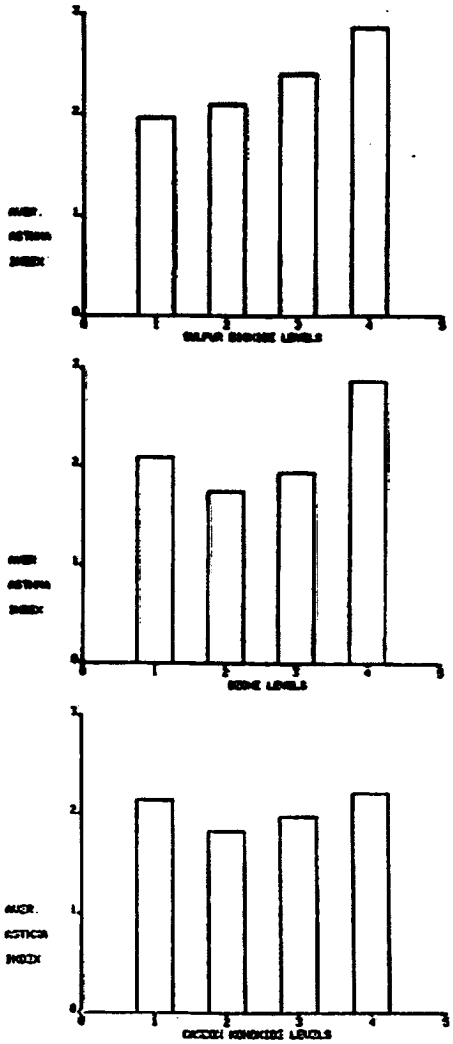
The severity of the air pollution levels presented in Figures 1-3 can be estimated by comparing these values with the California state air pollution standards for Stage 1 episodes.[6] Based on instantaneous maxima in parts per million (ppm): carbon monoxide = 50, sulfur dioxide = 3, ozone = 0.5, nitrogen oxides = 3. Based on one hour averaging times: carbon monoxide = 40, sulfur dioxide = 0.5, ozone = 0.2. During 1974 the following number of Stage 1 episode levels were attained in the Los Angeles basin: Carbon monoxide = 19, sulfur dioxide = 0, ozone = 84, nitrogen oxides = 6.

As a check to see whether the variance within each week would provide additional information, the daily averages of sulfur dioxide were plotted against their respective daily asthma index for the total patients (Figures 5-6). In addition we categorized the patients according to severity of symptoms and plotted the daily averages for these groups (Figures 7-9). We made this distinction since Carnow, et al[7] reported that 39 patients with severe bronchopulmonary disease over the age of 55 showed an increase in the acute morbidity rate in association with increased levels of sulfur dioxide. Visual examination of these plots also does not reveal any noticeable relationships. After plotting these single variables over time, a more controlled and quantitative evaluation of the data was made by matching each individual's daily Asthma Index with the daily pollution level in his/her residential zone.

Figures 10-12 illustrate the relationship between the average Asthma Index for all patients and the corresponding categorized pollution levels. Level of exposure was defined



Figures 7-9. Mean Asthma Index per day for patients grouped according to severity of symptoms. Note that the scale has been changed from the previous figures in order to accommodate the larger range of values



Figures 10-12. All graphs display averages of the Asthma Index scores grouped according to exposure to four levels of air pollutant concentrations (PPM). (July, 1974, to July, 1975)

Sulfur Dioxide: Level 1: .01, .02, .03, .04, .05
Level 2: .06, .07, .08, .09, .10
Level 3: .11, .12, .13, .14, .15
Level 4: .16, .17, .20, .26, .30

Ozone: Level 1: .01 - .09
Level 2: .10 - .18
Level 3: .19 - .27
Level 4: .28 - .37

Carbon Monoxide: Level 1: 1 - 11
Level 2: 12 - 22
Level 3: 23 - 33
Level 4: 34 - 56

as the daily air pollution reading (range) in the air monitoring zone where the patient resides. Data for days on which patients reported that they were out of town were excluded. These graphs appear to show a positive relationship between sulfur dioxide and ozone levels and the Asthma Index. However, these bar graphs are misleading since they do not take into account the variance and number of reports which comprise each level of pollutants.

As can be seen from Table I, one major problem with making conclusions based solely upon these bar graphs is that the number of reports which comprise each pollutant level varies. For example, the number of reports which correspond to pollution levels of 32 ppm, 34 ppm and 37 ppm of ozone is only 2, 2 and 1 respectively. Thus the three highest Asthma Index means (5.5, 6.5 and 5.0) make the average value for the Level 4 group high even though they reflect only a small percentage of the scores reported by that group. Furthermore, not only did these five reports come from only two patients but neither of these patients reported more asthma symptoms with increasing ozone concentrations. Pearson's correlation coefficient, which takes into account this variability, was less than .10 between each pollutant and the Asthma Index. In summary, then, if we had neglected to take into account the sample size and variance for each subgroup, we might have erroneously reported a positive relationship between exposure to increasing concentrations of ozone and an increase in asthma symptoms.

Table II illustrates that air monitoring zones may be high in one pollutant and very low in another. This makes it inappropriate in our study to evaluate the long-term effect of pollutants by

TABLE I. MEAN ASTHMA INDEX PER OZONE LEVEL BY GROUPS EXPOSED TO FOUR LEVELS OF OZONE CONCENTRATIONS.

	Ozone Level In PPM	Mean Asthma Index	Number of Reports
Level 1	.01	2.850	307
	.02	2.374	981
	.03	2.166	1401
	.04	2.058	1252
	.05	1.956	1104
	.06	2.058	791
	.07	1.842	822
	.08	1.978	712
	.09	1.822	443
Level 2	.10	1.601	489
	.11	1.854	424
	.12	1.671	426
	.13	1.779	335
	.14	1.634	372
	.15	2.082	243
	.16	1.898	196
	.17	1.956	183
	.18	1.554	242
Level 3	.19	1.581	105
	.20	1.802	131
	.21	1.869	99
	.22	1.913	115
	.23	1.912	80
	.24	2.135	96
	.25	2.364	33
	.26	2.241	54
	.27	2.414	29
Level 4	.28	2.162	37
	.29	2.850	20
	.30	2.600	20
	.31	1.250	20
	.32	5.500	2
	.33	2.385	26
	.34	6.500	2
	.36	1.571	7
	.37	5.000	1

TABLE II. RANK ORDER OF AIR MONITORING STATIONS ACCORDING TO AVERAGE CONCENTRATION OF POLLUTANTS.

	Sulfur Dioxide		Ozone		Carbon Monoxide		Nitrogen Oxides		Particulates	
Station	Aver. Conc.	Rank	Aver. Conc.	Rank	Aver. Conc.	Rank	Aver. Conc.	Rank	Aver. Conc.	Rank
1	.043	2	.097	5	14.2	1(H)	.420	1(H)	97	3
60	.032	5	.119	1(H)	6.4	7(L)	.213	7(L)	106	1(H)
69	.036	4	.103	3	13.3	2	.353	2	No Data	
71	.038	3	.068	6	9.5	6	.339	3	106	1(H)
74	.019	7(L)	.102	4	9.6	5	.328	5	84	5
83	.032	5	.116	2	12.4	4	.333	4	80	6(L)
84	.055	1(H)	.045	7(L)	13.2	3	.275	6	87	4

* Average of the Daily Instantaneous Maxima (In PPM) for July 1974–July 1975.
(L) =Station with lowest average concentration.
(H) =Station with highest average concentration.

categorizing residential zones into high and low zones since the sample size within each zone is not large enough to take into account the inverse relationships between these pollutants. In addition, Figures 1-3 show that the different pollutants reach peak concentrations during different seasons of the year.* Thus, since the total group of patients displays symptoms consistently year round, we cannot explain much of the variance in symptom patterns by relating symptoms to only one kind of pollutant. However, even when we used multivariate data analysis techniques, we still could not show significant relationships between these three pollutants and asthma symptoms. Tables III and V show the results of a step-wise multiple regression analysis[6] which we used as a means to construct a linear combination of independent variables which best predicts the dependent variable (Asthma Index). Four measurements are presented for each independent variable. The multiple R is the correlation between the dependent variable and the independent variable from the current and preceding steps. The simple R is the correlation between the independent and dependent variables. The B is the regression coefficient and the BETA is the normalized regression coefficient.

In addition we have done some preliminary analyses of animal exposure concurrently with the air pollution factors. Table IV shows the results of a test of the difference between severity of asthma symptoms (Asthma Index means) for the patients who did not own cats and dogs and those who owned cats and dogs (indoors and outdoors). The results of the data for the first six months (described in Part 1 of this series) and for the whole year (Table IV) show that patients who owned cats and dogs reported a significantly higher mean Asthma Index. This consistency between the data from the first six months and the whole year strengthens the hypothesis that constant exposure to these animals is related to the greater severity of their symptoms. As a means of measuring which variables are most strongly related to the Asthma Index, we performed the step-wise multiple regression analysis again (Table V), this time adding animal exposure to our list of independent variables. Results of these analyses indicate that a much greater percentage of the variance of the asthma symptoms can be accounted for by exposure to animals than to air pollutants.

Discussion

Previous studies on air pollution and asthma have produced conflicting results. Table VI illustrates some of

*The different characteristics of these pollutants (Figures 1-4 and Table I) can be explained by the fact that ozone is a "secondary" pollutant, whereas oxides of nitrogen and carbon monoxide are "primary" pollutants. Primary pollutants reach their peak right after emission, while secondary pollutants are by-products of reactions (e.g., photochemical) and reach their peak later in the day when they might have been carried by winds into a different zone. Also, "the highest average concentrations of ozone are measured during the months of June through October, when horizontal and vertical dispersion of auto emissions are limited and optimum sunshine is available."[6]

TABLE III. STEP-WISE MULTIPLE REGRESSION WITH THE ASTHMA INDEX AS THE DEPENDENT VARIABLE AND CARBON MONOXIDE, OZONE AND SULFUR DIOXIDE AS THE INDEPENDENT VARIABLES.

	MULTIPLE R	SIMPLE R	B	BETA
Carbon Monoxide	0.04809	-0.04809	-0.00505	-0.05374
Ozone	0.06996	-0.04652	-0.00484	-0.03852
Sulfur Dioxide	0.09034	0.03038	0.01872	0.06203

these results according to their respective research designs.

As can be seen from this table, Zeidberg et al[15] reported significant associations between ambient sulfur dioxide levels and asthma symptoms. They reported that ". . . when the attack rates on the thirty days of the highest SO_2 levels were compared with the rates on the forty-six days with the lowest levels, the difference in the respective rates of 0.130 and 0.110 was significant at the 5% level."[15] Two important points should be noted. First, the attack rate of 0.130 on days of high sulfation was lower than the average attack rate (0.133) for all days, irrespective of

TABLE IV. TEST OF DIFFERENCES BETWEEN RECODED ASTHMA INDEX MEANS FOR DATA FROM JULY, 1974 - JUNE, 1975.

	Mean Score of the Recoded Asthma Index or Each Patient Grouped According to Exposure to Animals		
	(1) No Animals	(2) Animals Inside the Home	(3) Animals Outside the Home
	0.125	0.520	3.448
	0.348	1.745	3.799
	0.137	5.869	2.382
	0.044	4.880	0.429
	1.976	0.962	1.946
	1.454	0.317	3.612
	0.157	6.350	0.475
	0.042	3.650	5.630
	4.104	4.627	5.543
	1.878	4.058	3.398
	0.035		5.623
	3.368		3.599
	1.154		
	1.137		
	0.308		
	0.248		
	0.148		
	2.298		
	0.905		
	3.015		
	1.470		
Mean	1.160	3.298	3.324
Std. Dev.	1.221	2.245	1.789
N	21	10	12

*$t_{1,2} = 3.455$ ($p < .005$)
*$t_{1,3} = 4.128$ ($p < .005$)
$t_{2,3} = 0.030$ ($p > .05$)

TABLE V. STEP-WISE MULTIPLE REGRESSION WITH THE ASTHMA INDEX AS THE DEPENDENT VARIABLE AND CARBON MONOXIDE, OZONE, SULFUR DIOXIDE, AND ANIMAL OWNERSHIP AS THE INDEPENDENT VARIABLES.

	Multiple R	Simple R	B	Beta
Carbon Monoxide	0.04809	-0.04809	-0.00505	0.05374
Ozone	0.06996	-0.04652	-0.00484	-0.03852
Sulfur Dioxide	0.09034	0.03038	0.01872	0.06203
Animal Owners	0.37832	0.37150	0.57197	0.36841

SO_2 levels. Second, a check of the graph (Figure 5, from Zeidberg, 1961) shows that the two peaks (maximum attack rates) for asthma attacks occur in October and May when SO_2 is near its minimum levels. From these observations it is difficult to accept that the difference between mean attack rates of 0.130 and 0.110 could be very meaningful. It would have been most helpful if standard deviations or at least the statistical tests used to verify

TABLE VI. SUMMARY OF PREVIOUS STUDIES ON EFFECTS OF AIR POLLUTION ON ASTHMA.

			Independent Variables					
Dependent Variable	Mode of Analysis	Investigator	CO	SO_2	Oxidants	Particulates	Dust	Poor Combustion Particle with Associated Silica
Visits to hospital for asthma	Day-by day association	Ribon, et al.[4]	-	-	-			
		Greenburg, et al.[9]	-	-				
		Goldstein, et al.[10]		(-+)				
		Lewis, et al.[11]						+
		Girsh, et al.[12]	±(?)	+(?)	+(?)	+(?)	+(?)	
	Frequency by residential zones	Sultz, et al.[13]				+		
	Day-by-day association	Schoettlin, et al.[14]						
Asthma symptoms via daily diary	Day-by-day association & frequency by residential zones	Zeidberg, et al.[15]		+				

- = Reported no significant associations
+ = Reported significant association
+(?) = Girsh, et al. "Could not incriminate any Specific pollutants."
(-+) = Goldstein, et al. found small, negative (partial) correlations in Harlem; but found strong positive (partial) correlations in Brooklyn. Since levels of sulfur dioxide were higher on the average in the Harlem area than in the Brooklyn area, they concluded: ". . we feel that in our case SO_2 is not necessarily the causative agent, but might rather implicate some other confounding variable . . ."

significance at the .05 level had been stated.*

Schoettlin and Landau[14] were the only investigators to report finding significant associations between ozone levels and asthma symptoms. They concluded from their study, which went from September through December of 1956, that a "significantly greater number of persons had attacks on days with high enough oxidant values to cause eye irritation (25 ppm) than on other days . . ." They did not provide in their report values for the means, number of people reporting each day and type of statistical test used. They also did not report whether the "25 ppm" criteria was based on instantaneous maxima or one-hour averaging times. This is especially important since, through correspondence with the Los Angeles Air Pollution Control District, we know that there were only five days during which 25 ppm was exceeded based on the one-hour averaging time, and 11 days based on the instantaneous maxima criterion. Thus at the best, 11 days were compared with 87 days and, at the worst, 5 days were compared with 93 days. It is also important to know that there were only three days in September and two days in October when ozone exceeded 25 ppm, based on the one-hour averaging time; while only seven days in September and four days in October exceeded this level based upon instantaneous maxima. Thus, since there were no "high oxidant" days in November and December, the data for the high versus low oxidant groups were sampled over different times of the year when other seasonal factors may have influenced the results. An even more important point is that the mean for each group should be based upon the proportion of persons reporting attacks (# of attacks/# of people reporting) per day. For example, since the number of persons reporting each day was not given, there may have been fewer persons reporting by November when there were no days on which ozone exceeded the criterion level. Thus this significant result, using the mean number of reported attacks, could actually be due to fewer persons turning in reports during the last month of the three-month study.

A major reason for our critique of the Zeidberg and Schoettlin articles is to clear up some of the confusion in the literature pertaining to effects of air pollution and asthma. Part of this confusion stems from authors who have cited the conclusions of these two studies without discussing any of the problems in the data analysis procedures and some who also have made erroneous statements about the results. For example, other authors who have cited the Schoettlin and/or Zeidberg studies as evidence for a relationship between air pollutants and asthma include Zweiman et al,[1] Girsh et al,[12] Lave et al,[17] Chiaramonte et al[18] and Salvaggio et al.[19].

Conclusion

In the preceding discussion we have shown not only that our own data do not indicate a strong association between air pollution and asthma but also that the two other studies which used daily diaries to measure asthma symptoms did not show convincing evidence either. In fact our data, combined with the studies listed in Table VI, indicate that at least as many epidemiological studies have found negative results as positive results.

In addition to the epidemiological studies by Ribon,[4] Greenburg,[9] and Goldstein,[10] recent laboratory investigations compare favorably with our results. For example, even though

*For a more detailed critique of this study see dissertation manuscript.[16]

Hackney et al included volunteers with a history of "hyper-reactive" airways in their study, they reported "no-detectable-effects" on pulmonary function tests and symptomatology at levels of 0.25 to 0.30 ppm of ozone.[20,21] However they found significant effects at 0.37 ppm of ozone. Our patients had only one exposure to a level as high as 0.37 ppm and, therefore, were probably not exposed to the ozone concentrations needed to produce noticeable effects.

This inability to show positive relationships, however, does not mean that these relationships do not exist. Factors which may have influenced our results include the following.

(1) The study of air pollutants is complicated by the fact that more than one pollutant may be important in asthma and peak concentrations of these different pollutants are often inversely related in terms of both residential zones and time of the year. For example, patients in a study may be classified as residing in the highest sulfur dioxide zone and at the same time unknowingly be in the lowest oxidant zone. Future studies should ensure that enough patients live in each residential area to adequately analyze the effect of these different pollutants.

(2) Patients may have adapted behaviorally and physiologically to the air pollutants. Behaviorally, patients may be staying indoors and reducing their participation in strenuous activities on smoggy days. Physiologically, recent studies[22] have indicated that Los Angeles residents may build up a tolerance to ozone. Also, D.L. Dungworth et al[23,24] have reported that although there is damage to the lungs of monkeys which were exposed to ozone concentrations greater than 0.5 ppm, the damage lessens when the exposure is below 0.5 ppm and disappears when the exposure is below 0.2 ppm. Since none of our patients were exposed to ozone concentrations greater than 0.37 ppm, this repair and adaptation which occurs below 0.5 ppm may be a reason why we did not detect any significant relationships between ozone concentrations and asthma symptoms.

(3) Patients selected for this study have been undergoing hyposensitization. Although this may have affected the frequency and severity of asthma symptoms, it was necessary to use these patients in order to ensure that our patients would be seen regularly.

(4) Patients may have been inaccurate in reporting their symptoms. We reduced the importance of this factor as much as possible by interviewing the patients at least once a month and collecting their reports weekly. In addition the consistency between our data and that from other studies reduces the likelihood that inaccuracy of reporting was a major problem.

(5) Particulates or other air pollutants may be more important than the pollutants that we studied.

(6) The subjects in our study may not have been exposed to the threshold levels of air pollutants required to detect their effects. Thus there is a strong possibility we did not find significant associations because other factors such as exposure to animals had greater immediate consequences than exposure to ambient levels of air pollutants.

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